AMENDMENTS TO THE CLAIMS

1. *(Currently Amended)* A computer-aided method of ~~identifying a ligand that binds to a protein~~ docking a ligand to a protein so as to determine ligand conformations likely to bind to said protein, said method comprising:

performing a pre-docking conformational search and generating multiple solution conformations of a ligand therefrom;

generating a binding site image of a protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one conformation of the multiple solution conformations of the ligand to initially position said at least one conformation of said ligand as a rigid body into said binding site so as to obtain at least one position of the ligand relative to the protein in a protein-ligand complex;

optimizing the at least one position of the ligand while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed;

calculating a score for the optimized position of the ligand using one or more potential functions ~~that is predictive of the ligand's potential to bind to the protein~~; and

~~identifying said ligand as a ligand that binds to said protein if said score is above a threshold~~

selecting one or more optimized ligand positions based on said score.

2. *(Previously Presented)* The method of claim 1, additionally comprising, after performing the pre-docking conformational search and generating multiple solution conformations, creating a database of the multiple solution conformations of the ligand and storing said three-dimensional database for subsequent use by said matching.

3. *(Previously Presented)* The method of claim 2, wherein said database of the multiple solution conformations of the ligand comprises a conformational database of a combinatorial library.

4.   *(Previously Presented)* The method of claim 1, wherein said performing the pre-docking conformational search and generating multiple solution conformations of the ligand comprises:

randomly generating a plurality of conformations of the ligand;

minimizing the strain of each conformation of the plurality of conformations;

using the strain and the solvent accessible surface area of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple conformations of the ligand in solution.

5.   *(Previously Presented)* The method of claim 1, wherein said generating the binding site image includes at least one of creating a list of apolar hot spots identifying points in the binding site that are favorable for an apolar atom to bind, and generating a list of polar hot spots identifying points in the binding site that are favorable for a hydrogen bond donor or acceptor to bind.

6.   *(Previously Presented)* The method of claim 5, wherein said generating the binding site image further comprises:

placing a grid around the binding site of the protein;

determining a hot spot search volume using said grid;

determining hot spots using a grid-like search of the hot spot search volume; and

for each type of hot spot, clustering the hot spots and retaining a desired number of top clusters of hot spots, said desired number of top clusters comprising said multiple hot spots to be employed by said matching.

7.   *(Previously Presented)* The method of claim 1, wherein said matching comprises:

matching atoms of the at least one solution conformation of the ligand to appropriate hot spots of the protein by positioning the at least one solution conformation of the ligand as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one solution conformation of the ligand into the binding site of the protein.

8.   *(Previously Presented)* The method of claim 7, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

$I(R,T)$ = rms deviation between a jth hot spot and a jth atom of the at least one solution conformation of the ligand;

H_j =   a position vector of a jth hot spot of the protein;

A_j =   a position vector of a jth atom of the at least one solution conformation of the ligand;

R =   a 3x3 rotation matrix; and

T =   a translation vector.

9.   *(Previously Presented)* The method of claim 1, wherein multiple positions of the ligand are obtained, and said optimizing step comprises :

eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the ligand and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

10.   *(Previously Presented)*   The method of claim 9, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.

11-20. *(Cancelled)*

21.   *(Currently Amended)*   At least one program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of ~~identifying a ligand that binds to a protein~~ docking a ligand to a protein so as to determine ligand conformations likely to bind to said protein, said method comprising:

       performing a pre-docking conformational search and generating multiple solution conformations of a ligand therefrom;

       generating a binding site image of a protein, said binding site image comprising multiple hot spots;

       matching hot spots of the binding site image to atoms in at least one conformation of the multiple solution conformations of the ligand to initially position said at least one conformation of said ligand as a rigid body into said binding site so as to obtain at least one position of the ligand relative to the protein in a protein-ligand complex;

       optimizing the at least one position of the ligand while allowing translation, orientation and rotatable bonds of the ligand to vary, and while holding the protein fixed;

       calculating a score for the optimized position of the ligand using one or more potential functions ~~that is predictive of the ligand's potential to bind to the protein~~; and

       ~~identifying said ligand as a ligand that binds to said protein if said score is above a threshold~~

       selecting one or more optimized ligand positions based on said score.

22.   *(Previously Presented)*   The at least one program storage device of claim 21, additionally comprising, after performing the pre-docking conformational search and generating multiple solution conformations of the ligand, creating a database of the multiple solution

conformations of the ligand and storing said three-dimensional database for subsequent use by said matching.

23.   *(Previously Presented)* The at least one program storage device of claim 22, wherein said database of the multiple solution conformations of the ligand comprises a conformational database of a combinatorial library.

24.   *(Previously Presented)* The at least one program storage device of claim 21, wherein said performing the pre-docking conformational search and generating multiple solution conformations of the ligand comprises:

randomly generating a plurality of conformations of the ligand;

minimizing the strain of each conformation of the plurality of conformations;

using the strain and the solvent accessible surface area of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple solution conformations of the ligand.

25.   *(Original)*   The at least one program storage device of claim 21, wherein said generating the binding site image includes at least one of creating a list of apolar hot spots identifying points in the binding site that are favorable for an apolar atom to bind, and generating a list of polar hot spots identifying points in the binding site that are favorable for a hydrogen bond donor or acceptor to bind.

26.   *(Previously Presented)*   The at least one program storage device of claim 25, wherein said generating the binding site image further comprises:

placing a grid around the binding site of the protein;

determining a hot spot search volume using said grid;

determining hot spots using a grid-like search of the hot spot search volume; and

for each type of hot spot, clustering the hot spots and retaining a desired number of top clusters of hot spots, said desired number of top clusters comprising said multiple hot spots to be employed by said matching.

27. *(Previously Presented)* The at least one program storage device of claim 21, wherein said matching comprises:

matching atoms of the at least one solution conformation of the ligand to appropriate hot spots of the protein by positioning the at least one solution conformation of the ligand as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one solution conformation of the ligand into the binding site of the protein.

28. *(Previously Presented)* The at least one program storage device of claim 27, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R,T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

I(R,T) = rms deviation between a jth hot spot and a jth atom of the at least one solution conformation of the ligand ;

$H_j =$ a position vector of a jth hot spot of the protein;

$A_j =$ a position vector of a jth atom of the at least one solution conformation of the ligand;

$R =$ a 3x3 rotation matrix; and

$T =$ a translation vector.

29. *(Previously Presented)* The at least one program storage device of claim 21, wherein multiple positions of the ligand are obtained, and said optimizing step comprises :

eliminating each position of the ligand having a predetermined percentage of atoms with a steric clash;

ranking remaining positions of the ligand using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the ligand and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the ligand to vary.

30.   *(Previously Presented)* The at least one program storage device of claim 29, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the ligand to vary.